During the 1861 secession debates, Greene County was mostly Unionist, but Tusculum College students were divided. Before the June secession vote, then-U.S. Sen. Johnson spoke in Greeneville in support of the Union. Afterward, secessionist students burned Johnson in effigy and raised a Confederate flag over Old College. Confronted by a professor loyal to the Union, a student helped lower the flag, for which his classmates called him “Benedict Arnold.” The administration suspended classes and students went home.

The college suffered during the war as both Federal and Confederate forces camped in and around the building. In July 1865, college trustees reported: “The late war has left Tusculum College in a deplorable condition—its enclosures are broken down, its library much wasted and abused and its chemical and philosophical apparatus broken and destroyed.” Another local institution, Greeneville College, suffered so much that its campus was sold for a mere $700 after the war and its library was sent to Old College. In 1868, the two schools merged as Greeneville and Tusculum College, using the rooms and facilities at Old College.